

Remarks

Page 2 of the description has been amended to provide statements of invention corresponding to the enclosed claims. The brief description of the drawings which appears on pages 2 and 3 of the description as originally filed is replaced by a more detailed description of the drawings using information taken from the text material on the drawings as originally filed.

The drawing sheets are replaced in response to the ISA's comments regarding drawing defects. Figure 2 is now labelled Figs. 2A - 2D. The enclosed amended drawings do not contain the text matter found on the drawings as originally filed, which has now been imported into the description in the "Brief Description of the Drawings". Page 16 has been amended at line 21 thereof to refer to Figures 2A-D (rather than Figure 2) in view of the drawing amendment.

Multiple dependencies have been added to certain of the claims. New claim 1 corresponds to original claim 1, except that it is in Swiss-style form, rather than being a method of treatment claim. New claim 1 also specifies the use of 4-hydroxyisoleucine, rather than hydroxylated amino acids in general. Support for this change to claim 1 can be found, for example, in original claim 2. New claim 1 also specifies particular types of antidiabetic compounds used in combination with 4-hydroxyisoleucine. Support for this aspect of new claim 1 can be found, for example, at page 3, lines 11-16, and page 5, line 14 through page 11, line 18.

The claims that depend from new claim 1 are now in Swiss-style and correspond to those which depended from original claim 1, as follows. New claim 2 corresponds to original claim 3; new claim 3 corresponds to original claim 4; new claim 4 corresponds to original claim 5; new claim 5 corresponds to original claim 6; new claim 6 corresponds to original claim 7; new claim 7 corresponds to original claim 8; new claims 9-12 correspond to the identically numbered original claims; and new claim 13 corresponds to original claim 14. New claim 8, which specifies the use of an insulin-sensitizing agent, is supported, for example, at page 7, line 7 through page 8, line 2 of the application.

New claim 14 corresponds to original claim 15, except that it specifies the presence of 4-hydroxyisoleucine in the kit, rather than hydroxylated amino acids in general. Support for this change can be found, for example, in original claim 16. New claim 14 also specifies particular types of antidiabetic compounds used in combination with 4-hydroxyisoleucine, and support for this aspect of new claim 14 can be found, for example, at page 3, lines 11-16, and page 5, line 14 through page 11, line 18.

New claims 15-20 correspond to original claims 17-22, respectively, while new claims 22-27 correspond to original claims 23-28, respectively. Support for new claim 21, which specifies the presence of an insulin-sensitizing agent, is supported in the application at, for example, page 7, line 7 through page 8, line 2.

New claim 28 is drawn to a pharmaceutical composition that corresponds to the pharmaceutical kit specified in claim 14, while new claim 29 specifies the use of the claimed pharmaceutical kits and compositions in the treatment of diabetes in a patient. New claims 30-42 are method of treatment claims that correspond to new claims 1-13, respectively. New claim 43 corresponds to original claim 13.

The remaining objections raised in Boxes V and VIII of the Written Opinion are addressed as follows.

### Novelty

Claims 1-4, 13-18, and 27 were deemed to lack novelty under PCT Article 33(2) over document D1 on the basis that this document discloses the use of 4-hydroxyisoleucine in combination with insulin. In response to this objection, we note that the new independent claims (1, 14, and 28) specify 4-hydroxyisoleucine in combination with one or more additional antidiabetic agents selected from a list that does not include insulin. The claims that do specify the use of insulin (new claims 3, 16, and 30) do so in a manner requiring the presence of 4-hydroxyisoleucine and an additional, non-insulin antidiabetic agent, which document D1 does not teach. Thus, we submit that this objection does not apply to any of the new claims.

### Inventive Step

Claims 1-28 were deemed to lack an inventive step over the combination of documents D2-D6. In particular, the Written Opinion states that the problem to be solved by the present invention is to provide a hydroxylated amino acid and an antidiabetic agent combination therapy for the treatment of diabetes, and notes that three documents disclose the insulinotropic and antidiabetic effects of 4-hydroxyisoleucine, as well as the use of this compound in the treatment of type II diabetes (D2, D4, and D5). Further, the Written Opinion states that document D3 discloses the insulinotropic activities of other hydroxylated amino acids in a diabetic animal model, and that document D6 discloses the use of glucagon-like peptide 1 (GLP-1) analogs for treating diabetes.

Based on the cited documents and the state of the art with regard to antidiabetic agents, the Written Opinion states that it would have been obvious to one skilled in the art to combine 4-hydroxyisoleucine with other antidiabetic agents, such as the GLP-1 analogs of document D6, for treating diabetes. Further, it is stated that it would have been obvious to make such combinations with other hydroxylated amino acids, in light of the teachings of document D3, and that the combination of two or more known antidiabetic agents in pharmaceutical kits is not considered to involve an inventive step. Applicants respectfully disagree.

At the outset, we note that the present applicants have shown, for the first time, that use of combinations of 4-hydroxyisoleucine with other particular antidiabetic agents leads to unexpectedly beneficial effects. For example, the experiments described at page 15, line 18 through page 17, line 6 showed a trend indicating that a combination of 4-

hydroxyisoleucine and a thiazolidinedione (rosiglitazone) may be more effective with respect to glucose tolerance in mice rendered hyperglycemic by consuming a high fat diet. This finding is important, because the observed effects indicate that dosages of thiazolidinediones may be decreased when administered with 4-hydroxyisoleucine, which is beneficial because of toxicity issues associated with thiazolidinedione administration. In another example, on page 17, line 8 through page 18, line 11, experiments are described which showed that a combination of 4-hydroxyisoleucine and a sulfonylurea compound (glibenclamide) led to an enhanced effect in an *in vitro* insulin secretion assay relative to the results obtained by use of either compound alone. Further, in an experiment described on page 18, line 13 through page 19, line 11, the combination of 4-hydroxyisoleucine and Exendin-4 were found to have enhanced effects on insulin secretion in an *in vitro* assay, as compared to either agent alone.

Turning now to the specific details of the objection, we first note that the new claims specify 4-hydroxyisoleucine, and not other hydroxylated amino acids. Thus, the reference to document D3 is not relevant. Further, we submit that combinations such as those of the present invention show an inventive step over the prior art. In particular, the fact that the drugs can each be used to treat the same condition (diabetes) on their own does not mean that those of skill in the art would conclude that the drugs could advantageously be used in combination, as applicants have found, for example, in the experimental results described above. Just because two drugs are both known to be useful in the treatment of a disease does not mean that it can be concluded that, for example, a combination of these drugs may lead to an additive effect. If it were possible to generalize in this manner, then that would mean that it would be expected that combining multiple drugs that each have a small effect on a condition would cure the condition, provided that a sufficient number of drugs were included in the combination, and this certainly is not true. Although it is not uncommon for drug combinations to be used in the treatment of certain diseases, including diabetes and related conditions, the finding of additive effects is simply not predictable, based solely on the premise that the drugs are used to treat the same disease. Thus, because there is no suggestion of the claimed combinations in the art, and because there would not have necessarily been an expectation of improved effects, as the present applicants have observed, applicants respectfully submit that the objection for lack of inventive step should be withdrawn.

#### Claim Defects

The Written Opinion notes that claims 1 and 15-28 do not comply with PCT Rule 6.3(a), on the basis that what was deemed to be the technical feature of the invention, 4-hydroxyisoleucine and its use in treating diabetes, is absent from these claims. In response to this objection, we note that the new claims all require the use or presence of 4-hydroxyisoleucine. Thus, this objection should not be made with respect to the new claims.

We note that the International Preliminary Examining Authority may not provide an opinion with respect to industrial applicability of enclosed claims 30-43. Nevertheless,

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we respectfully submit that an opinion with respect to novelty and inventiveness may still be established based on the use of the medicaments referred to in these claims.

Should the Examiner continue to have any concerns regarding novelty and inventiveness or any technical defects in the specification, the Examiner is respectfully requested to issue a further Written Opinion and/or contact the undersigned with a view to placing this application in good form for receipt of a positive opinion.

Yours very truly,  
SMART & BIGGAR

J. Christopher Robinson

JCR/jlj  
Encl.